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# Methods for assessing diabetic polyneuropathy: validity and reproducibility of the measurement of sensory symptom severity and nerve function tests

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## Abstract

The usefulness of sensory symptoms in the assessment of diabetic polyneuropathy is unclear. In the present study, we studied the hypothesis that pain is associated with small nerve fibre function, and that sensory alteration is associated with large nerve fibre function. In addition, we assessed the reproducibility and the ability to detect changes in clinical status over time of the nerve function tests currently used in clinical trials. Patients (78) with stable diabetic polyneuropathy were examined on three separate occasions with a test–retest interval of 17 and 52 weeks. Small nerve fibre function was measured using temperature discrimination thresholds for warmth (TDT<sub>warmth</sub>) and cold (TDT<sub>cold</sub>). Large nerve fibre function was measured by testing sensory and motor nerve conduction velocities (SNCV and MNCV) and vibration perception thresholds (VPT). Neuropathic pain was only significantly associated with TDT<sub>cold</sub>, and with the MNCV of the tibial nerve. Sensory alteration was associated with almost all nerve function tests except the SNCV and MNCV of the ulnar nerve. The measurements of symptom severity and the nerve function tests all proved to be sufficiently reproducible. The standardized smallest detectable difference on group level (SDD) of the measurement of sensory alteration and neuropathic pain were almost the same (9% and 12%, respectively). Among the nerve function tests, the SNCV and MNCV had the smallest SDD (3–4%), and were, therefore, potentially the most responsive instruments. The SDD of the TDT was greater than the VPT (9–14% vs 21–28%, respectively). In conclusion, neuropathic pain was not associated with small nerve fibre function, and sensory alteration was associated with both large and small fibre function. In addition, the standardized measurement of symptom severity, the SNCV and MNCV tests, and the VPT test appear to be useful for monitoring the course of polyneuropathy in clinical trials. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

**Keywords:** Diabetic polyneuropathy; Sensory symptoms; Nerve function tests

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## 1. Introduction

Polyneuropathy is a very common complication of diabetes mellitus that is frequently accompanied by distressful sensory symptoms [1]. Polyneuropathy is considered to be a major causal factor in the majority of foot ulcerations in diabetic patients [2,3]. The incidence of foot ulceration can be reduced if polyneuropathy is diagnosed at an early stage [4–6].

In daily clinical practice, sensory symptoms are often the reason for a diabetic patient to consult his physician [7]. However, the usefulness of measuring sensory symptoms in the assessment of polyneuropathy in daily clinical practice is unclear, because lack of clarity exists about the relationship between nerve function and symptom severity of polyneuropathy.

Recently, by means of a questionnaire, we have established the existence of two dimensions of sensory symptoms in patients with diabetic polyneuropathy [8,9]. In addition to a dimension of neuropathic pain, there appeared to be a dimension of sensory alteration complaints, which included paraesthesiae. It was also demonstrated that the latter was predominantly associated with nerve dysfunction, irrespective the type of nerve fibre damage [8]. The existence of this relationship is potentially of great clinical importance, because it indicates that enquiring about sensory alteration complaints may be useful in the assessment of diabetic polyneuropathy in daily clinical practice. However, the origin of the existence of the two separate dimensions of sensory symptoms is still unclear. Previous reports have shown that neuropathic pain may be caused by small nerve fibre damage [10–13]. Furthermore, it has been shown that painless neuropathy and foot ulceration was associated with large nerve fibre abnormality [14]. Therefore, we hypothesized that the severity of neuropathic pain is associated with small nerve fibre damage, and that the severity of complaints of sensory alteration is associated with large nerve fibre damage.

Several methods are currently used for the assessment of small and large nerve fibre function. In consensus meetings, both the testing of nerve conduction velocities and the testing of vibration

perception thresholds (VPT) are recommended as valid and reproducible tests for assessing large nerve fibre function, and the testing of warm and cold thermal discrimination thresholds ( $TDT_{warmth}$  and  $TDT_{cold}$ , respectively) is recommended for the assessment of small nerve fibre function [15–18]. For this reason, these tests were used for the assessment of nerve function in the present study.

The outcome of the nerve conduction velocity tests, VPT and TDT, can be influenced by many external factors. In order to ensure the reproducibility of the tests, they must be performed in a standardized manner. However, reproducibility of the tests might differ among centres [18]. Moreover, when the course of polyneuropathy is monitored, as happens in clinical trials, the methods chosen to assess nerve function and symptom severity must not only be reproducible, but should also be able to detect changes over time in patients. However, there is very little published data on the ability of tests of nerve conduction velocities, VPT and TDT to detect changes of nerve function [19].

The first aim of this study was to assess the (construct) validity of the measurement of the severity of neuropathic pain and sensory alteration complaints. Therefore, we investigated whether the severity of neuropathic pain was predominantly associated with small nerve fibre function, and the severity of sensory alteration complaints was predominantly associated with large nerve fibre function. In addition, we studied the reproducibility (test–retest reliability) and the ability to detect changes over time both of the measurement of sensory symptom severity and of the tests of nerve conduction velocities, VPT and TDT.

## 2. Materials and methods

### 2.1. Patients

A total of 78 patients participated in the study. Inclusion criteria for entering the study were: insulin-dependent (Type 1) or non-insulin dependent (Type 2) diabetes mellitus, treated with in-

sulin for a period of at least 6 months; age 20–65 years; familiarity with home glucose monitoring and self-regulation; stable metabolic control of diabetes; established polyneuropathy defined as at least one abnormal nerve conduction velocity under the 5th-percentile (P5-value) of normal aged-matched controls [20], together with an abnormal value of the VPT or  $TDT_{warmth}$  measured at the foot above the P95-value of normal aged-matched controls [21–23].

Excluded from participation in the study were patients with other putative causes of polyneuropathy, using neurotoxic drugs, neuropathic foot ulcerations or arterial insufficiency in the legs.

The study duration was 52 weeks. Patients were asked to visit the research ward at the start of the study, and again after 17 and 52 weeks. For each patient the assessments were made by the same investigator throughout the study and at the same time of day, using the same instruments.

### 3. Nerve function tests

#### 3.1. Small nerve fibre function

Thermal thresholds were assessed at the ventral side of the left wrist with a temperature threshold tester (Medelec Triple T, Old Woking, UK). The two alternative forced-choice method was used to measure the temperature discrimination threshold for warmth ( $TDT_{warmth}$ ) and cold ( $TDT_{cold}$ ). The TDT was expressed as the change from the basic skin temperature in °C detected by the patient. Details of this testing procedure have been described elsewhere [21,22].

#### 3.2. Large nerve fibre function

Vibration perception threshold (VPT) expressed in  $\mu m$  was assessed at the dorsum of the second metacarpal bone of the left hand and the dorsum of the first metatarsal bone of the left foot. The VPT was measured using a Vibrometer (Somedic, Stockholm, Type 4). The amplitude of a probe, vibrating at 100 Hz, was increased from zero and the subject was asked to indicate the moment when he or she started to feel the vibration

(method of limits). Details of this testing procedure have been described elsewhere [23,24].

Sensory nerve conduction velocity (SNCV) of the right ulnar nerve and left sural nerve was measured antidromically using surface electrodes. Because at the baseline measurements sural nerve action potentials could only be evoked in 32 patients (41%), this nerve function measurement was not included in the analysis. Motor nerve conduction velocity (MNCV) of the left tibial nerve and right ulnar nerve was recorded using surface electrodes over the abductor hallucis and digiti minimi muscles, respectively. Motor and sensory nerve conduction velocities were measured and expressed in m/s. The limbs were heated in a warm bath for 30 min before the examination was carried out, and during the examination skin temperature was maintained at 34°C.

#### 3.3. Assessment of symptom severity

The Diabetes symptom checklist-Type 2 (DSC-Type 2) was used to measure the severity of sensory symptoms [9]. This instrument consists of 34 questions about diabetes-related symptoms. It has a 10-item sensory polyneuropathy dimension, sub-divided into two different sub-dimensions, including six questions on sensory alteration: (1) tingling sensations in the hands/fingers; (2) numbness of the hands; (3) strange sensation in the legs or feet; (4) tingling sensation in the lower legs; (5) numbness of the feet; (6) tingling sensation in the arms/legs at night, and four questions on neuropathic pain: (7) shooting pains in the legs; (8) burning pains in the legs; (9) pain in the legs during walking; (10) burning pain in the calves at night. By means of this checklist the frequency of occurrence of the symptoms was measured. The possible answers were scored as: 0 = not at all, 1 = one or more times a month, 2 = one or more times a week and, 3 = daily. The sum of the scores of the frequency of occurrence of the symptoms was computed as a measure of severity. This outcome varied between 0 (no symptoms) and 18 (severe symptoms) for the sub-dimension of sensory alteration, and between 0 and 12 for the sub-dimension of neuropathic pain.

3.4. Laboratory examinations

In the course of the study an attempt was made to maintain stable glycaemic control. Glycosylated haemoglobin (HbA<sub>1c</sub>) was used as a parameter of glycaemic control. In order to exclude the possible influence of changes in glycaemic control on symptoms and nerve function, HbA<sub>1c</sub> was measured every eight weeks ( $\pm 2$  weeks), during the course of the study.

3.5. Statistical analysis

A logarithmic transformation ( $\log_{10}$ ) was carried out in order to normalize the distribution of the outcome of the VPT and TDT assessments. To investigate the stability of nerve function during the course of the study, the mean of the test–retest differences and the standard deviation of these differences in the MNCV of the tibial nerve and TDT<sub>warmth</sub> were computed.

Construct validity was determined by assessing the correlation between the tests of small and large nerve fibre function, on the one hand, and neuropathic pain and sensory alteration on the other hand, and was assessed by using Pearson correlation coefficients.

The test–retest reproducibility was expressed in two ways. First of all, Pearson correlation coefficients were calculated between the baseline and follow-up measurements. Subsequently, the smallest detectable statistical significant mean difference in test outcome over time, within a group of 100 patients, was assessed based on the estimated variance in test–retest differences. This was calculated by using a sample-size formula, as proposed by Guyatt, and was expressed as the

smallest detectable statistically significant test–retest difference (SDD) on group level, with the assumption that  $\alpha = 0.05$ ,  $\beta = 0.10$  and group size = 100.[25] Using the sample size formula, the SDD of the tests in groups of other sizes (i.e. 50) can easily be computed.

Sample size formula: 
$$SDD = \sqrt{\frac{(Z\alpha + Z\beta)^2 \times \sigma^2}{N_t}}$$

SDD is the smallest detectable statistically significant mean test–retest difference measurements over time in groups;  $\sigma^2$  is the variance of intra-person difference over time between subjects, estimated by  $SD_{dif}^2$ , the calculated standard deviation of intra-subject differences between test and retest;  $\alpha = 0.05$  ( $Z\alpha = 1.96$ );  $\beta = 0.10$  ( $Z\beta = 1.282$ ); and  $N_t = 100$  (group size).

In order to permit comparison between the SDD of the different tests of nerve function, the SDD was also expressed as the percentage of change for the corresponding mean of the pooled data of test and retest.

4. Results

Table 1 lists the characteristics of the patients participating in the study. The number of patients for whom data were available in Tables 2 and 3 was less than 78, for several reasons: three patients discontinued before the end of the study because they no longer wished to co-operate; thirteen questionnaires were missing at baseline and 12 questionnaires at 17 weeks, because they were not returned; for two of the returned questionnaires the total score could not be calculated, because one or more of the questions had not been answered.

According to repeated HbA<sub>1c</sub> measurements, metabolic control was stable during the course of the study. The mean HbA<sub>1c</sub> (%) at 17 weeks was 8.3 (range 4.9–12.8), and the mean HbA<sub>1c</sub> (%) at 52 weeks was 8.2 (range 5.5–12.8).

The nerve function of the patients was stable during the course of the study. The mean of the differences of test and retest of the MNCV of the

Table 1  
Patient characteristics

<i>n</i>	78
Mean age (years) <sup>a</sup>	49.5 (range 27–65)
Gender (m/f ratio)	43/35
Mean diabetes duration (years) <sup>a</sup>	21.3 (range 1–46)
Mean HbA <sub>1c</sub> (%) <sup>a</sup>	8.3 (range 5.1–13.0)

<sup>a</sup> Measured at baseline.

Table 2

Pearson correlations between symptom severity and nerve fibre function at baseline<sup>a</sup>

<i>N</i>		Symptom severity			
		Sensory alteration		Pain	
				<i>r</i>	<i>P</i> -value
		<i>r</i>	<i>P</i> -value	<i>r</i>	<i>P</i> -value
<i>Large nerve fibre function</i>					
MNCV <sub>tibial</sub>	57	−0.43	0.001	−0.29	0.03
MNCV <sub>ulnar</sub>	63	−0.23	0.06	−0.21	0.07
SNCV <sub>ulnar</sub>	61	−0.16	0.23	−0.10	0.23
VPT <sub>foot</sub>	63	0.30	0.02	−0.16	0.20
VPT <sub>hand</sub>	62	0.26	0.04	−0.14	0.30
<i>Small nerve fibre function</i>					
TDT <sub>warm</sub>	62	0.53	0.0001	0.16	0.22
TDT <sub>cold</sub>	62	0.33	0.009	0.26	0.04

<sup>a</sup> *n*, number of patients for whom data were available. MNCV: motor nerve conduction velocity, expressed in m/s; SNCV: sensory nerve conduction velocity, expressed in m/s; VPT: vibration perception threshold, expressed in  $\mu\text{m}$ , <sup>10</sup>log-transformed; TDT: temperature discrimination threshold assessed at the left wrist and expressed in  $^{\circ}\text{C}$ , <sup>10</sup>log-transformed.

Table 3

Test–retest reproducibility and smallest detectable difference (SDD) on group level of symptom severity and nerve function tests, performed at baseline and follow-up at 17 weeks

	<i>n</i> <sup>a</sup>	Mean (IQR) <sup>b</sup>	Reproducibility		SDD	(% <sup>c</sup> )
			Test–retest correlation <sup>c</sup>	SD <sub>diff</sub> <sup>d</sup>		
Sensory alteration	59	8.81 (4.0–12.0)	0.89	2.58	0.84	(9)
Pain	60	4.83 (2.0–6.5)	0.85	1.76	0.57	(12)
MNCV <sub>tibial</sub>	67	38.74 (35.5–42.0)	0.70	4.43	1.44	(4)
MNCV <sub>ulnar</sub>	74	55.46 (52.5–59.1)	0.56	5.84	1.89	(3)
SNCV <sub>ulnar</sub>	71	44.71 (42.5–48.0)	0.67	4.11	1.33	(3)
VPT <sub>foot</sub>	75	1.07 (0.69–1.34)	0.77	0.31	0.1	(9)
VPT <sub>hand</sub>	74	0.28 (0.18–0.32)	0.92	0.11	0.04	(14)
TDT <sub>warm</sub>	73	0.33 (0.14–0.44)	0.76	0.21	0.07	(21)
TDT <sub>cold</sub>	73	0.25 (0.10–0.33)	0.49	0.22	0.07	(28)

<sup>a</sup> Number of patients for whom the data were available.

<sup>b</sup> Mean and inter-quartile range of the pooled data of test and retest.

<sup>c</sup> Pearson correlation coefficient.

<sup>d</sup> Standard deviation of the within-subject differences between the two measurements, SDD, smallest detectable test–retest difference over time within groups (*n* = 100).

<sup>e</sup> SDD standardized to corresponding mean of the pooled data of test and retest. MNCV: motor nerve conduction velocity, expressed in m/s; SNCV: sensory nerve conduction velocity, expressed in m/s; VPT: vibration perception threshold, expressed in  $\mu\text{m}$ , <sup>10</sup>log-transformed; TDT: temperature discrimination threshold, expressed in  $^{\circ}\text{C}$ , <sup>10</sup>log-transformed.

tibial nerve and the TDT<sub>warmth</sub> was very small and did not significantly differ from zero (data not shown). Moreover, the standard deviation of the test–retest differences was relatively small (Table 3).

#### 4.1. Construct validity of the measurements of symptom severity

The associations between the measurements of symptom severity on the one hand, and nerve

function on the other hand, assessed at baseline, are presented in Table 2. The sub-dimension of sensory alteration was correlated with almost all nerve function tests, except the SNCV and MNCV of the ulnar nerve. The sub-dimension of neuropathic pain was only correlated with the MNCV<sub>tibial</sub> and the TDT<sub>cold</sub>. Therefore, sensory alteration unexpectedly not only performed better with regard to large nerve fibre function, but also with regard to small nerve fibre function.

#### 4.2. Reproducibility

The reproducibility of the assessment of sensory symptom severity and nerve function tests, for the test–retest interval of 17 weeks, is presented in Table 3. The test–retest correlation coefficients of the assessments of the severity of sensory alteration complaints and neuropathic pain were 0.89 and 0.85, respectively. Test–retest correlation coefficients of nerve function tests were between 0.49 and 0.92. The figures for the test–retest interval of 52 weeks were almost the same (data not shown). The reproducibility of the symptom severity-scale was scarcely influenced by the length of the test–retest interval. The test–retest correlation coefficient for sensory alteration was 0.89 for the interval of 17 weeks, and 0.81 for the interval of 52 weeks. The test–retest correlation coefficient for neuropathic pain was 0.85 for the interval of 17 weeks, and 0.78 for the interval of 52 weeks. The test–retest reproducibility figures of the nerve function tests were also scarcely influenced by the length of the test–retest interval. Test–retest correlation coefficients of the nerve function tests, for the interval of 52 weeks, were between 0.46 and 0.97 (data not shown). The only nerve function test that was influenced by the length of the test–retest interval was the MNCV<sub>tibial</sub>. The test–retest correlation coefficients were 0.70 and 0.46, for the intervals of 17 and 52 weeks, respectively.

For the assessments of symptom severity and nerve function tests the SDD was calculated for the outcomes of test and retest at baseline compared to 17 weeks, and baseline compared to 52 weeks. The SDDs of the measurements of symptom severity and nerve function tests, for the test–retest interval of 17 weeks, are presented in

Table 3. The SDD (standardized to the corresponding mean of test and retest, group size = 100) of the assessment of sensory alteration was almost the same as the SDD of the assessment of neuropathic pain (percentage of difference for the corresponding mean: 9% vs 12%). The SDDs of the assessments of nerve conduction velocities were smaller than the SDDs of the assessments of VPT, and the SDDs of the assessments of VPT were smaller than the SDDs of the assessments of TDT. The difference percentages for the corresponding mean were 3–4% for nerve conduction velocities, 9% and 14% for VPT, and 21% and 28% for TDT. The figures for the test–retest interval of 52 weeks were similar (data not shown). The SDDs of both the assessments of symptom severity and the nerve function tests, were not influenced by the length of the test–retest interval of 17 and 52 weeks, respectively.

#### 5. Discussion

There is no ‘gold standard’ available for the assessment of polyneuropathy. Therefore, we examined the construct validity of the measurement of symptom severity, by calculating the correlations between the outcomes of a number of tests of small and large nerve fibre function and symptom severity. The nerve function tests we used, have been recommended as valid and reproducible measurements of the severity of polyneuropathy [15–18]. Moreover, we have confirmed that the reproducibility of the nerve function tests was also acceptable when they were performed in our research centre. Therefore, we were able to use these tests for the construct validation of the measurement of symptom severity.

In the literature, it has been suggested that painful and painless neuropathy are two separate clinical conditions. Therefore, theoretically, we expected small nerve fibre function to be associated with the severity of neuropathic pain, and large nerve fibre function to be associated with the severity of symptoms of sensory alteration [10–14]. However, in the present study, pain was not found to be predominantly associated with small nerve fibre function, and sensory alteration was

not found to be predominantly associated with large nerve fibre function. Our results are in keeping with previous reports of nerve biopsy studies on this issue [26,27]. In these studies, a typical pattern of nerve fibre damage or regeneration of nerve fibres in diabetic painful polyneuropathy could not be demonstrated.

Yet, it remains uncertain whether small and large fibre involvement in diabetic polyneuropathy are two separate clinical conditions, or whether the small and large fibre type represent either side of a continuous spectrum of fibre damage [28,29]. However, an explanation of our results could be, that we included a high percentage of patients with an advanced stage of nerve damage. At baseline, the measurement of SNCV<sub>sural</sub> was not possible in 59% of the patients. This is suggestive for advanced nerve damage and therefore, the included patients might have been beyond the stage of painful small nerve fibre polyneuropathy. This explanation of our results is in keeping with the paper of Benbow et al. In that paper, in a prospective study, it was demonstrated that neuropathic pain tends to improve with time and small nerve fibre function continues to deteriorate. They concluded that measures of small nerve fibres do not predict the evolution of painful symptoms [30].

The results in our study do show however, that sensory alteration performed better than neuropathic pain with regard to both large and small nerve fibre function. This is an indication that the sensory alteration sub-scale is more useful for the assessment of diabetic polyneuropathy in daily clinical practice than the neuropathic pain sub-scale.

We also assessed reproducibility, including the SDD in a group of 100 patients, and the influence of the length of the test–retest interval on these test-characteristics of the measurement of neuropathic symptom severity and of nerve function tests. Insight into the reproducibility and SDD of tests is important, because these test-characteristics can directly influence the conclusions drawn from clinical trials. In a stable patient-population with polyneuropathy the outcome of nerve function testing should also be stable. However, if the clinical status of polyneuropathy improves, e.g.

due to medication, a change should be detected. During the course of the present study, the nerve function of the patients remained stable. Therefore, in order to assess the ability of the tests to detect changes in clinical trials, we assessed the SDD in a group of 100 patients. The SDD is a measurement of reproducibility within certain groups of patients. A test with a poor reproducibility has a large SDD, in which case the ‘signal’ has to be relatively loud to overcome the ‘noise’. It is, therefore, probably only able to detect relatively large intervention effects in clinical trials.

The results of the present study indicate an acceptable degree of reproducibility of the assessment of symptom severity, using the DSC-Type 2, and of the nerve function tests. The influence of the length of the test–retest time interval on the reproducibility of almost all tests appeared to be small. Only for the MNCV measurements of the tibial nerve a longer test–retest time interval reduced reproducibility according to the correlation coefficients. This is a surprising finding because we performed the test procedure in the same standardized manner for both MNCV measurements. In addition, in literature, especially nerve conduction studies are recommended because of their reliability [18]. Therefore, it could be a chance finding which remains subject to confirmation from other studies.

A good test–retest correlation of a test does not always implicate a good performance concerning its smallest detectable statistical significant difference on group level that is standardized to the corresponding mean of the tests. This is clearly demonstrated in Table 3. The test–retest correlation of the MNCV of the ulnar nerve in comparison to the TDT<sub>warmth</sub> is 0.56 and 0.76, respectively, with a SDD standardized to the corresponding mean of 3% and 21%, respectively.

The assessments of symptom severity, using the DSC-Type 2, proved to have a small SDD. Therefore, the standardized measurement of symptom severity is a useful method of monitoring the course of polyneuropathy in clinical trials. With regard to the nerve function tests, the testing of nerve conduction velocities proved to have the smallest SDD. The testing of the TDT<sub>warmth</sub> and the TDT<sub>cold</sub> turned out to have a larger SDD than



the testing of VPT. This finding was consistent for both test–retest intervals. In addition, several previous reports pointed out that the reproducibility of TDT testing is poor when compared to VPT testing [18,24]. Therefore, the TDT might be less useful than the nerve conduction velocity tests and the VPT for monitoring the course of polyneuropathy in clinical trials.

Symptoms of polyneuropathy and nerve function may be influenced by changes in the level of glycaemic control. [31,32] In the present study a possible influence of glycaemic control on the outcomes of the study was minimized because, according to HbA<sub>1c</sub> measurements, a stable glycaemic control was maintained during the course of the study.

In conclusion, we found no indication that pain was predominantly associated with small nerve fibre function, or that sensory alteration was predominantly associated with large nerve fibre function. However, sensory alteration showed a stronger and more consistent association than neuropathic pain with the measurements of both large and small nerve fibre function. Therefore, the assessment of the severity of sensory alteration can be useful in the assessment of polyneuropathy in daily clinical practice.

The standardized assessment of symptom severity, using the DSC-Type 2, as well as the nerve function tests, proved to be sufficiently reproducible. Moreover, according to the SDD, the measurement of symptom severity can be useful for monitoring the course of polyneuropathy in clinical trials. Furthermore, of the nerve function tests studied, the TDT testing appears to be less useful than the nerve conduction velocity testing and VPT for monitoring the course of polyneuropathy in clinical trials.

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